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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,389	07/07/2003	Susan Boyce	T1453CA	7398

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,389	BOYCE ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/6/05;7/7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 6, 2005 and July 7, 2003 have been received and acknowledged.

Status of Claims

Claims 1-26 are cancelled and claims 27-34 are new.

Claims 27-34 are pending in this office action.

Specification

The amendment to the specification has been received and the disclosure to the claims a continuation of 09/700,776 claiming priority to the application a 371 National Phase entry of international application number PCT/GB99101632 filed May 19, 1999 which claims priority under 35 U.S.C. 119 from GB Application No. 9810920.0, filed May 21, 1998. has been entered and acknowledged.

Claim Objections

Claims 27 and 28 are objected to because of the following informalities: The abbreviation COX-2, NK-1 and CNS should be given as its full name or with the full name in parenthesis therewith when first used. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to

practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

Applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a representative number of specific compounds.

In other words, the Applicant has not described with sufficient clarity a selective cycloxygenase-2 inhibitor (COX-2) contemplated nor exemplified and does not inform the public of the limits of the monopoly asserted.

II. Claims 27-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a representative number of specific compounds.

In other words, the Applicant has not described with sufficient clarity the neurokinin-1 (NK-1) receptor antagonist contemplated nor exemplified and does not inform the public of the limits of the monopoly asserted.

III. Claims 27-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a representative number of specific compounds.

In other words, the Applicant has not described with sufficient clarity the pharmaceutically acceptable carrier or excipient contemplated nor exemplified and does not inform the public of the limits of the monopoly asserted.

IV. Claims 29-31 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating inflammatory disorders such as hyperalgesia a form of inflammatory disorder with a selective Cox-2 inhibitor that has an IC_{50} that is ≤ 40nM or ≤ 20nM and a NK-1 inhibitor 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)- ethoxy)-3-(S):i4-fl uorophenyl)-4-(3-(5-oxo- 1H,4H-1,2,4-triazolo)methyl)- morpholine and 2-(R)-(1-(R)'(3,5- bis(trifiuoromethyl)phenyl)ethoxyi-4-(5-(N,N-dimethylamino)methyl-l,2,3- triazol-4-yl)methyl-3-(S)-phenylmorpholine, does not reasonably provide enablement for such a broad use of every representative of NK-1 receptor antagonist with a selective COX-2 inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

In the instant case, applicants are claiming a method of preventing inflammatory disorder in a patient administering an amount of a COX-2 inhibitor and an amount of a NK-1 receptor antagonist is capable of preventing every inflammatory disorder in a patient.

1) Nature of the invention.

The nature of the invention is a method of preventing inflammatory disorder in a patient administering an amount of a COX-2 inhibitor and an amount of a NK-1 receptor antagonist is capable of preventing every inflammatory disorder in a patient.

As stated, however, claim 32 recites that any or a large representation of inflammatory disorders are intended with any NK-1 receptor antagonist and a selective COX-2 inhibitor is capable of preventing inflammatory disorders.

2) State of the prior art and the predictability or lack thereof in the art.

Applicants' specification (see page 47 lines 15+) indicates large number compounds (I-XII), of synthetic compounds. Discovering a candidate drug involves repeating the same test for several screening of a hundreds to several million times. This requires a great deal of reproducibility from the test. In order to obtain the state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease) and in what combinatory ratio desire to see inhibitory effect. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between every disease claimed as capable of being treated by the broad use of the NK-1 compounds and selective COX-2 inhibitor of the instant claims, one of skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of the disease.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation as mentioned above. One of skill in the art would first need to determine the type of inflammatory disorder to be treated, and then determine which of the numerous NK-1 receptor atagonist and selective COX-2 inhibitors would be suitable for said treatment and/or prevention.

4) Level of predictability in the art.

As disclosed above, treating one disorder does not necessarily result in treating series of related disorders or symptoms even in view of the seemingly high level of skill in the art. Firstly, for a compound or genus to be effective against a disease associated with inflammatory disorders generally is contrary to medical science. Inflammatory disorder is a process that can take place in virtually any part of the body. There is a vast range

of forms that it can take causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which every or even most, inflammations arise.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found on pages 48-57 wherein foot-tapping in Guinea pigs and Ferrets were used to identify and evaluate pain.

6) Existence of working examples.

Applicant's limited working example does not enable one of skill in the art to treat the numerous amounts of diseases encompassed by the instant invention with the numerous variation of the COX-2 inhibitor and NK-1 receptor antagonist.

7) Breadth of claims.

Claims 29 and 32 are extremely broad due to the vast number of possible diseases encompassed by the instant invention and the vast number of possible variation of the compounds.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of any disease. As a result necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in instant claims, with no assurance of success.

This rejection can be overcome by reciting specific closely related diseases with the specific selective COX-2 inhibitors and NK-1 receptor antagonist compound.

The following is a quotation of the second paragraph of 35 U.S.C. 112:second

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the use of the pharmaceutical composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 27 and 29-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Talley et al. US 5,859,257.

Talley teaches with regards to the pharmaceutical composition a selective Cox-2 inhibitor (see col. col. 4 lines 45+) used in combination with a NK-1 receptor antagonist (see col. 4, lines 30+) with atleast one pharmaceutically acceptable carrier (see col. 21, lines 3+) to treat inflammatory disease such as rheumatoid arthritis (see col. 3, lines 2-6) as in claims 29, 30, 32 and 33. With regards to claim 29, Cox-2 and NK-1 are co-administered to treat inflammatory disorders by administering an effective amount to the patient the combination is administered to give relief is taught (see col. 98, lines 27+).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Talley et al. US 5,859,257 in view of Gardner et al. Regulatory Peptides 65(1996) 45-53.

Talley teaches with regards to the pharmaceutical composition a selective Cox-2 inhibitor (see col. col. 4 lines 45+) used in combination with a NK-1 receptor antagonist (see col. 4, lines 30+) with atleast one pharmaceutically acceptable carrier (see col. 21, lines 3+) to treat inflammatory disease such as rheumatoid arthritis (see col. 3, lines 2-6) as in claims 29, 30, 32 and 33. With regards to claim 29, Cox-2 and NK-1 are co-administered to treat inflammatory disorders by administering an effective amount to the patient the combination is administered to give relief is taught (see col. 98, lines 27+). Talley et al, however did not teach that the neurokinin-1 receptor antagonist is a CNS penetrant nor orally active.

Gardner et al. teach the use of a neurokinin-1receptor antagonist of compounds of formula 10 to treat inflammation in general (see page 52 last para. highlighted) that is orally active (see abstract) and is a CNS-penetrant (see page 52 highlighted sec.) Although, Talley et al did not teach that the NK-1 receptor antagonist is orally active and a CNS-penetrant as in claims 28, 29 and 34. However, one of ordinary skill in the art would be motivated to combine the teachings of Talley et al with that of Gardner et al. use a neurokinin-1 receptor antagonist that is a CNS-penetrant and is used in the treatment of inflammatory disorders, substitute the NK-1 receptor antagonist of Gardner with that of Talley and used in combination with a selective COX-2 inhibitor for the treatment of inflammatory disease such as rheumatoid arthritis as taught by Talley et al. with expectation of success because the Talley et al. teach that COX-2 inhibitors are used with NK-1 receptor antagonist to treat inflammatory disorders.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
9/19/06

Ardin H. Marschel 9/29/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER